REMARKS

Claims 1-17, 19-32, 52-57, 59, 73, and 76-92 are currently pending in the present application.

Applicants note that the Examiner has withdrawn objections to the drawings and specification and to claims 3 and 30 due to minor informalities or typographical errors. The rejection of claims 5-6, 8, 11-12, and 26-27 under 35 U.S.C. §112, second paragraph has also been withdrawn.

Claim 1 has been amended to recite "the recombinant protein variant" after the second occurrence of "naturally occurring allergen." Support for this amendment may be found throughout the specification and particularly in original claims 1, and 52-54.

Claims 25-26 and 30-32 have been amended to include reference to Accession Numbers. Support for these amendments may be found in the specification on at least pages 30 and 32.

Claims 52-54 have been amended to recite "comprises two or more primary mutations spaced by at least one non-mutated amino acid residue." Support for this amendment may be found throughout the specification and in original claims 1 and 19.

No new matter has been introduced in these amendments. Entry and consideration of these amendments is respectfully requested.

Amendments To The Specification

The specification has been amended at page 30, line 16; and at page 31, line 13 to replace "Q76H" with "E76Q." Support for this amendment may be found in the specification on page 30 and in Fig. 21 where residue 76 is described as being glutamic acid (E) in the reference sequence Accession No. AJ488060.

The Rejections Under the Second Paragraph of 35 U.S.C. § 112 Should Be Withdrawn

Claims 1-17, 19-32, 52-57, 59, 73, and 76-92 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office Action indicates that claim 1 is

indefinite because the term "protective immune response" has been defined broadly by Applicants. In response, Applicants respectfully point out that the term "protective immune response" (the complete term recited in pending claim 1) is particularly defined in this application, as it is used in the vaccine art. *See*, in particular, in the application as originally filed at page 43, lines 1-7. This definition makes it clear that the term, as used in this application, specifically refers to responses resulting in the production of mediator substances, such as cytokines and antibodies, that is well known to occur upon the stimulation of leukocytes (including T and B lymphocytes) and whose production neutralizes a particular antigen. Applicants therefore submit that the term is fully definite within the context of the application.

With regard to IgE antibodies mentioned by the Examiner, Applicants point out that IgG antibodies (and not IgE antibodies) are the ones that are generated in response to the inventive recombinant proteins and the IgG antibodies play a role in providing the desired protective immune response of the present invention. Additionally, the Examiner states that Applicants' definition also involves the activation of T cells, and that the number of stimulated T-cells necessary to raise a "protective" immune response is not discussed. Applicants note that there is no need to describe any particular number of T-cells or B cells that are stimulated using the inventive recombinant proteins. Applicants note that there are many examples throughout the specification of the use of "protective" consistent with its definition and as it is used in the vaccine art, for example with reference to the published application:

para 37: Introduction of mutations in the scaffold protein, introducing or modulating or eliminating existing antibody binding surface contours or epitopes homologous to structures of the allergen, results in creation of stable protein variants, ***capable of raising a protective immune response*** and with a lowered risk of inducing side-effects, since the mutated scaffold protein variant exhibits a lower antibody reactivity compared to the natural allergen.

"The purpose is to generate surface contours of the scaffold protein having similarity to the naturally occurring allergen in question, in order to enable stimulation of immune responses that will generate ***protective IgG antibodies*** with the ability to block IgE binding to the natural allergen and thereby alleviate or cure allergy symptoms."

para 42: The affinities of the IgE interactions should be reduced to a level limiting or abolishing the risk of triggering effector cell degranulation, while at the same time retaining the capacity to induce formation of ***protective antibodies reactive with the allergen*** in question.

para 79: The idea behind the invention is thus that a relatively small number of mutations are generally required in order to partly or fully establish allergen specific IgE recognizing contours on the surface of an appropriate scaffold protein. Such molecules have the potential ***of inducing new protective immune responses*** that can compete with IgE binding upon allergen exposure leading to a reduced risk of inducing IgE-mediated allergic responses

para 168: ***Protective immune response***: Raising a protective immune response means to alter the reaction of the immune system towards a naturally occurring allergen in order to avoid the adverse effects associated with allergy. The protective immune response is thought to be mediated largely by generation of a large number of IgG antibodies that presumably block the interaction between allergen and IgE antibodies. A protective immune response most likely also involves stimulation of T-cells.

The Examiner also alleges that with regard to claim 1, it is unclear what purpose is met by introducing an identical amino acid into a scaffold protein. We note that ***the identical amino acid reference is to the allergen***, and not the scaffold protein and believe that the Examiner is confused about the nature of the inventive recombinant protein. To arrive at the inventive recombinant proteins, a scaffold protein is initially selected that has a similar 3-D structure to the allergen, next the desired substitution mutations are introduced into the scaffold protein. These substitution mutations are selected and designed to be incorporated into the scaffold protein, based upon the corresponding sequence of the allergen. The substitutions introduce a mutation into the scaffold protein, which mutation/s correspond to either the same amino acid at the analogous position in the allergen, or a homologous amino acid residue of the analogous position in the allergen (would be a conservative change). The inventive recombinant proteins ***do not*** encompass recombinant scaffold proteins that are identical to the allergen, instead the inventive recombinant proteins are ***modified scaffold proteins***-- not identical to the native scaffold protein or to the naturally occurring allergen.

Additionally, the Examiner believes that the term "homologous" referring to an amino acid is unclear. Applicants point the Examiner to the definition for "homologous amino acid" provided in the specification at page 48, lines 15-23, and more specific definitions are provided throughout the Examples, in particular on pg 59, lines 5-7, pg. 60, lines 12-14, and lines 32-34 for Example 2.

The Examiner has rejected claims 25, 28, and 30-32, asserting that they are unclear due to the absence of SEQ ID NOs or a specific protein sequence reference. In the previous response, Applicants noted that these are dependent claims, and the base claims identify the reference proteins

as either Mal d 1 or Dau c 1. However, the Examiner has asserted that the claims are still not clear since there are several isomers of each protein and suggests adding reference to the specific amino acid sequence being mutated. Applicants point out that the mutations apply equally to isomers as to the reference protein, since the amino acid residues will be numbered in the same manner for the isomers. However, in order to expedite prosecution, Applicants are amending claims 25 and 29 to recite "wherein the *Mal d* 1 scaffold is *Mal d* 1 2620 with Accession No. AJ488060." Similarly, claims 30-32 have been amended to recite "wherein the Dau c1 has Accession No. T14325". Support for these amendments may be found on pages 30 and 32 of the specification.

The Examiner asserts that claim 26 recites an unclear mutation at position 76. Applicants note that this typographical error is actually in claim 25, and it has been amended to recite "E76Q" Support for the amendment may be found in the reference sequence described on page 30 of the specification. Applicants have corrected this error in two occurrences in the specification as noted in the remarks section above.

Finally, the Examiner alleges that claims 52-54 are unclear since they are drawn to variant proteins that have a primary mutation in a scaffold protein and that this mutated amino acid is either identical or homologous to a corresponding residue on the naturally occurring antigen. Applicants point the Examiner to the explanation provided above, which also applies to claims 52-54. Importantly, the claims do not encompass recombinant scaffold proteins that are identical to the allergen. Instead the inventive recombinant proteins are ***modified scaffold proteins***-- not identical to the native scaffold protein or to the naturally occurring allergen.

For all the foregoing reasons, Applicants respectfully submit that the rejections for indefiniteness under 35 U.S.C. § 112, paragraph 2, have been fully obviated and should be withdrawn.

The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Examiner has maintained the rejection of claims 1, 5-6, 9-10, 20-22, 55-56, and 59 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,583,046 to Valenta *et al.* ("Valenta"). Claims 1, 5-6, 8-9, 15, 20-24, and 52 have also been rejected under 35 U.S.C. § 102(b) as anticipated by Son *et al.*, Eur. J. Nutr., 1999, 38:201-215 ("Son"). In addition, the Examiner has

rejected claims 54 and 73 under 35 U.S.C. § 102(b) as anticipated by the publication of King *et al.*, J. Immun., 2001, 166(10):6057-6065 ("King").

A. The Legal Standard of Anticipation

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See M.P.E.P. §2131 (8th Ed. Rev. 2, May 2004). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must literally present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984).

B. Valenta Does Not Anticipate the Pending Claims

Valenta does not teach the use of a modified scaffold protein with a similar three-dimensional folding pattern to that of a desired natural allergen, nor does Valenta teach the insertion of mutations in the scaffold protein as recited in claim 1. Valenta teaches recombinant allergen proteins. In contrast, the present invention teaches the use of a scaffold protein which maintains the three-dimensional folding pattern of the allergen, and the introduction of point mutations into the scaffold protein, not into the allergen itself. Applicants note that the present claims do not encompass recombinant scaffold proteins that are identical to the allergen. Instead, the inventive recombinant scaffold proteins are modified when compared to the unmodified scaffold protein (i.e. the template) as well as when compared to the naturally occurring allergen.

Additionally, the claims require that the recombinant protein exhibit increased affinity and/or binding capacity to IgE antibodies specific to the naturally occurring allergen. Valenta does not teach recombinant mutant proteins that meet this requirement. Valenta does not teach recombinant proteins with structural similarity, *i.e.*, proteins with a similar tertiary structure. Applicants note that the Valenta results from IgE immunoblots are indicative only of binding conferred by an antigen binding site. *See* Valenta, col. 3, line 56 to col. 4, line 9. Having similar binding may or may not be due to a protein having an overall similar 3-D structure; it may be conferred by a protein with an antigenic site that confers this binding, while the protein does not

have a similar 3-D structure to the reference or native protein. Thus, Valenta does not require the three-dimensional folding pattern that the claims of the present invention require.

Furthermore, the polypeptides of Valenta have the same or similar antigenicity as the native allergen, *i.e.*, their binding affinity to IgE antibodies specific for the native allergen is the same or similar and do not exhibit increased binding. *See* col. 3, lines 17-30. The Examiner alleges that Valenta teaches:

> the results of IgE immunoblots, cross-inhibition tests, clinical tests and Northern (RNA) blots' and that these results 'indicate this invention provides polypeptides which exhibit the same or similar antigenicity as the related P14 pollen allergens of birch, alder, hazel, etc.[] The use of the term 'similar' suggests that the polypeptides are not completely identical in antigenicity, therefore being similar can comprise an increase in affinity or binding capacity (Fig. 1B, 13).

The terms "the same" or "similar" do not and cannot mean improved binding, which is greater binding. Additionally, the results cited by the Examiner are not quantitative tests (Fig. 1B and Fig. 13 is a dark immunoblot).

The present invention, on the other hand, claims recombinant proteins with an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring antigen. *See*, for example, page 28, lines 10-21 Accordingly, Valenta does not teach all of the elements of the rejected claims, because it does not teach increased binding to IgE, Valenta cannot anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under Valenta be withdrawn.

C. Son Does Not Anticipate the Pending Claims

The Examiner argues that Son teaches recombinant protein variants derived from Mal d 1 and Bet v 1. Applicants respectfully submit that Son does not teach all of the elements of the present invention. Son merely teaches, at best, the use of native allergens in which point mutations are inserted. See pages 202, and 204-205. In contrast, the present invention teaches the ***use of a scaffold protein*** which ***maintains the three-dimensional folding pattern of the allergen***, and ***the introduction of point mutations into the scaffold protein***, not into the allergen itself. See page 11, lines 15-27. In further contrast to the present invention, although Son teaches that point

mutations inserted into the native allergen can cause a reduction in IgE binding capacity (see page 208), Son does not teach that mutations inserted into a scaffold protein would increase or decrease the binding affinity of IgE specific to the native allergen. See page 24, line 26 to page 25, line 16. Insertion of point mutations according to the method of Son creates a risk of destabilizing the three-dimensional structure of the molecule. *Id.*

In particular, we note that the Son mutants are Ser112Pro, Ser111Cys, or Ser111Pro mutants. However, these mutations are ***not*** identical or homologous to the corresponding amino acid residues, and therefore do not satisfy that requirement of Applicants' pending claims. Indeed, Son actually teaches that these mutations are not homologous. For example, Son hypothesizes, on page 214 of that reference, that serine may be part of an epitope. Son then goes on to note that "proline is known to cause major structural changes in the protein fold, and the drastically decreased IgE reactivity of the proline mutants may also reflect major changes in the tertiary fold of the allergens." Likewise, the Ser111Cys mutant is likely to have a structural change compared to the native Mal d 1 isoform. Thus, in contrast to the Examiner's assertion that the single point mutations of Son have a decreased risk of destabilizing the three-dimensional structure of the scaffold protein, the reference actually contemplates major structural changes due to a single proline substitution.

Applicants' specification teaches that mutations from Serine to either Cysteine or Proline are not homologous substitutions. *See*, for example, in the specification at page 48, lines 15-23; on page 59, lines 5-7; on page 60, lines 12-14 and 32-34; in Example 2; and throughout the Examples. In contrast to Son, the present invention is directed to the introduction of mutations that preserve the three dimensional structure of the protein. See page 11, lines 15-27.

Accordingly, Son does not teach all of the elements of the rejected claims, and therefore does not anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under Son be withdrawn.

D. King Does Not Anticipate the Pending Claims

The Examiner argues that King teaches modified recombinant allergens consisting of a "host protein" which is used as a scaffold protein, which is fused with a "guest allergen." Applicants

would like to point out that claim 54 has been amended (inadvertently omitted in the previous response) to recite "comprises two or more primary mutations spaced by at least one non-mutated amino acid residue," as is recited in the other independent claims. Analogous amendments have been made in claims 52 and 53. Applicants note that King is directed to hybrid constructs wherein a scaffold protein is substituted with relatively long stretches of amino acids of a native allergen, and therefore does not contain "two or more primary mutations spaced by at least one non-mutated amino acid residue." Neither King nor Applicants' recombinant proteins would encompass the native allergen itself.

In view of the present amendments, King does not teach all of the elements of the rejected claims, and therefore does not anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under King be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,
By

Samuel S. Woodley, Ph.D.
Registration No.: 43,287
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant